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(54) Title: ENANTIOMERS OF 4-(5-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

(57) Abstract

Optical isomers of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and pharmaceutically acceptable salts thereof, their use and preparation are described. Both isomers are potent in the treatment of cognitive disorders.

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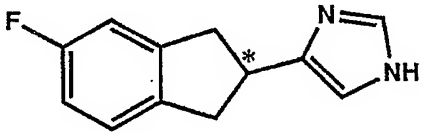
ENANTIOMERS OF 4-(5-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

The invention provides new optical isomers of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and pharmaceutically acceptable salts thereof, their use and preparation. Both optical isomers are potent in the treatment of cognitive disorders, although somewhat different pharmacological profiles may be ascribed to them. The (-)-enantiomer is the preferred one of the two enantiomers because it has a wider therapeutic window than the (+)-enantiomer. It is a very powerful antagonist of α_2-adrenoceptors without any α_1-agonism whereas the (+)-enantiomer is a moderate antagonist of α_2-adrenoceptors and a full α_1-agonist. Both enantiomers have good peroral bioavailability.

Valuable α_2-adrenoceptor antagonist have been disclosed earlier e.g. in the European patent publications No. 183492, 247764 and 372954. PCT patent publication No. 91/18886 discloses the use of some indan-imidazole derivatives, especially atipamezole, in the treatment of age-related memory impairment and other cognitive disorders. International patent application No. PCT/FI92/00349 describes a group of new long-acting 4(5)-substituted indan-imidazole derivatives which are useful in the treatment of cognitive disorders. One of these indan-imidazole derivatives is the racemate of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole which has an asymmetric carbon atom in the position 2 of the indan ring:



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The optically active enantiomers of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole may be prepared e.g. by conversion of racemic 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole into a mixture of diastereoisomers and separating these by fractional crystallization. Since 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole is a base, it may be converted into diastereoisomer salt mixture by reaction with an optically active acid, preferably with L-(+)- or D-(-)-tartaric acid. The diastereoisomers may be separated by repeated crystallization e.g. from water.

Once the diastereoisomers have been separated the acid addition salts may be converted back to the free bases by making their aqueous solutions alkaline with a base (e.g. sodium hydroxide) and by extracting the liberated base into an appropriate organic solvent.

The (-)- and (+)-enantiomers of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole react with organic or inorganic acids to form the corresponding acid addition salts, which have the same therapeutic activities as the bases. They can thus form many pharmaceutically useful acid addition salts such as chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates.

The racemate of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole may be prepared e.g. by nitrating 4-(2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride with a strong nitrating agent such as ureanitrate in the presence of sulfuric acid and thereafter reducing the nitro compound to the corresponding amino compound e.g by catalytic hydrogenation using PtO_2 or Pd/C as catalysts. The amino substituted compound is further converted to the corresponding diazonium fluoroborate with sodium nitrite in fluoboric acid at lowered temperature. The diazonium fluoroborate is then decomposed thermally to yield the racemate of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole.

The compounds according to the invention may be administered enterally or parenterally. In the treatment of cognitive disorders the preferable daily dosage is from 0.1 to 10 mg/kg, especially preferably from 0.2 to 1 mg/kg.

The acute toxicity (LD_{50}) for both enantiomers is about 100 mg/kg in mice (p.o.) and about 50 mg/kg in rat.

The pharmaceutical carriers which are typically employed with the compound of the invention may be solid or liquid and are selected with the planned manner of administration in mind. Choosing the auxiliary ingredients for the formulation is routine for those of ordinary skill in the art.

1. The α–adrenoceptor selectivity in vitro

α_2-Antagonism was determined by means of isolated, electrically stimulated prostatic portion of rat vas deferens preparation (Virtanen et al, Arch. Int. Pharmacodyn et Ther., 297, 190-204, 1989). In this model, α_2-agonist (detomidine) blocks electrically stimulated muscular contractions and the effect

of the α_2-antagonist is seen by administering it prior to the agonist and by determining its pA_2 value. The known α_2-antagonist atipamezole was used as a reference substance.

To obtain information also on the selectivity of the antagonist between α_1- and α_2-receptors, its ability to inhibit or stimulate α_1-receptors was determined by means of isolated epididymal portion of rat vas deferens. To determine α_1-antagonism, muscular contraction was induced by phenylephrine and the pA_2 value of the studied compound was determined as above. α_1-Agonist effect is presented as the pD_2 value (negative logarithm of the molar concentration of the compound producing 50 percent of maximal contraction). The results are given in Table 1.

Table 1. The selectivity of racemic 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and its enantiomers in comparison with atipamezole

Compound	α_2-Antagonism (pA_2 vs detomidine)	α_1-Antagonism (pA_2 vs phenyl-ephrine)	α_1-Agonism (pD_2)
(-)-enantiomer	9.1	6.7	no effect
(+)-enantiomer	7.9	not tested	6.0 full agonist
racemate	8.0	not tested	5.5 partial agonist
Atipamezole	8.0	5.0	no effect

2. Effects on memory

The effect of the (-)-enantiomer on learning and memory in linear arm maze task in rats was studied. The linear arm maze is a modified version of radial arm maze, which is a generally used memory test in rats. The (-)-enantiomer hydrochloride (0.1 mg/kg s.c.) was dissolved in distilled water. Water was also used as control. All injections were made in a volume of 1 ml/kg.

Apparatus: The maze was a wooden platform in a shape of two crosses one after another. The stem (starting arm) was 90 cm long and 12 cm wide. The

five other arms (goal arms) were 50 cm long and 12 cm wide. Four goal arms were situated perpendicularly to the stem and to the fifth arm which located opposite to the stem. On either side of the stem and the arms were edges, 2.0 cm high. At the end of each goal arm a hole 1 cm deep and 3 cm in diameter, served as a food cup. The starting platform (20 x 20 cm) was separated from the stem by a guillotine door. The door was 12 cm high and 7 cm wide. The door frame was 20 cm high and 20 cm wide. The maze was elevated 31 cm above the floor, in a low-lighted test room which contained other objects as well as the test apparatus. The holes at the end of the goal arms were baited with three pellets of prize food (45 mg pellets Bio Serve Inc.).

Procedures: Two days prior to training, animals were placed on a food deprivation scedule that reduces their body weights to 90% of initial weights. During these days the rats were habituated to handling (three times/day), test room and prize food. On the second day they were also habituated to the unbaited maze: three to five animals from the same cage at the same time for ten minutes. On the third day the goal arms were baited, and the teaching trial, one rat at a time, was carried out. The rat received drug or distilled water and 60 minutes later it was placed in the starting platform. After ten seconds the door was opened and the rat was allowed to explore the maze until all the baits were found. Reentries into an arm previously visited during that session were counted as errors. The time to find all the baits and correct choices made until the first mistake was recorded. At this time (teaching), every rat was allowed to stay in the maze for at least five minutes. On the next day the proper memory and learning testing began and continued for four days (testing days 1 to 4). Rats were given eight trials, two per day. Inter trial interval was 50 minutes. The drug or distilled water were administered 30 minutes before the first trial of the day. Otherwise testing trials were identical to the teaching trial. There were 20 animals in both groups.

Statistical analysis: The results were expressed as mean errors/trial, mean correct choices/trial and mean time/trial (seconds).The analysis of variance for the repeated measurements (ANOVA) was used to compare the effects of the drug and the testing day on learning and memory.

The results: The effects of the (-)-enantiomer on learning and memory are presented in the Figures 1, 2 and 3. The drug decreased the number of errors i.e. reentries into the arms already visited during the same trial (Fig 1). The (-)-enantiomer also increased the number of correct choices made before the first

error of the trial (Fig 2). These are thought to mean an effect on working memory and on the ability to concentrate on the trial, respectively. The drug also tended to decrease the time to solve the task (Fig 3). It is considered as an effect on speed to make decisions, in this case the correct choices. The number of errors and time decreased and the number of correct choices increased trial by trial which indicates learning also in the control group. There were no group x trial interactions, which means that the effect of the (-)-enantiomer did not depend on the trial. These results suggest that the (-)-enantiomer has learning and memory enhancing effects on adult rats.

3. The preparation of the optically active isomers

Racemic 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

Concentrated sulphuric acid (58 ml) was cooled to -10°C and the mixture of 4-(2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride (Karjalainen, A. J. et al U.S. 4,689,339; 13.8 g, 0.0625 mol) and ureanitrate (7.70 g, 0.0625 mol) was added in small portions to the acid solution at -10°C. After the reaction the solution was poured onto ice. The solution was made alkaline and extracted three times with ethyl acetate. The organic extracts were combined, dried and evaporated to dryness. The yield 13.0 g, 91 % of 4-(2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole.

Reduction of 4-(2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole to 4-(5-amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was carried out by adding 1.0 g of 10% palladium on carbon to 11.7 g (0.0512 mol) of 4-(2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole in 100 ml of ethanol and shaking the mixture in a hydrogen atmosphere at the room temperature. When the reduction came to a standstill the catalyst was removed. The filtrate was concentrated to give 9.63 g (94 %) of 4-(5-amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole. The product was purified by flash chromatography eluting with methylene chloride - methanol (9.5:0.5).

A flask containing fluoboric acid (48 wt. % solution in water, 120 ml) and 9.50 g (0.0475 mol) of 4-(5-amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was placed in an ice-salt bath and cooled to 0 °C. A solution of 3.30 g (0.0478 mol) of sodium nitrite in 10 ml of water was run in slowly while the temperature was kept at 0 °C. The mixture was stirred for an hour at 0 °C and then for an hour at the room temperature. The reaction mixture was evaporated twice to dryness with toluene. The thermal decomposition was

carried out in a flask which was heated with an electric heating mantle. When the generation of white fumes of boron trifluoride ceased the heating was stopped. The crude product was dissolved in methanol, the solution was filtered and evaporated to dryness. The yield of the crude 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was 9.51 g, 99 %. The product was purified by flash chromatography (the eluent methylene chloride - methanol 9.5:0.5).

^{1}H NMR (300 MHz, CD_3OD): δ 2.96-3.08 (2H, m, one H-1 and one H-3), 3.19-3.27 (2H, m, another H-1 and another H-3), 3.68 (1H, quintet, $^3J_{HH}$ 8.3 Hz, H-2), 6.80-6.86 (1H, m, H-6), 6.83 (1H, s, im-5), 6.92 (1H, dd, $^3J_{HF}$ 8.9 Hz, $^4J_{HH}$ 2.4 Hz, H-4), 7.16 (1H, dd, $^3J_{HH}$ 8.1 Hz, $^4J_{HF}$ 5.3 Hz, H-7), 7.59 (1H, s, im-4)

Separation of the enantiomers

D-(-)-Tartaric acid (0.44 g, 0.00293 mol) was dissolved in 2.5 ml of water at 60 °C. The racemate of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (I, 1.03 g, 0.00509 mol) and 178 µl of concentrated hydrochloric acid were added at 60 °C. The mixture was stirred at 60 °C until it became a clear solution. The solution was allowed to cool slowly. The precipitates were collected and recrystallized five times from water to give the D-(-)-tartaric acid salt of the (-)-enantiomer: mp 186-187 °C.

The D-(-)-tartaric acid adduct of the (-)-enantiomer was dissolved in water at 60 °C and ethyl acetate was added. The solution was made alkaline (pH 10) with diluted sodium hydroxide. The ethyl acetate phase was separated and the water phase was extracted twice with ethyl acetate. The combined organic phases were washed with water. Ethyl acetate was evaporated to dryness and the residue was crystallized from ethyl acetate. The product was filtered by suction and washed with cold ethyl acetate: mp 139 °C (DSC), specific rotation at 20 °C in methanol solution -3.7° (c=20 mg/ml).

The (-)-enantiomer base was dissolved in ethyl acetate and filtered by Millipore. The filtrate was made acidic (pH 1) with dry hydrochloric acid - ethyl acetate solution and cooled to -10 °C. The precipitate was filtered by suction and washed with ethyl acetate. Recrystallization from ethyl acetate gave the hydrochloride salt of (-)-4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole as a white crystalline solid: mp 191 °C (DSC); chromatographic purity 99.8 %

(HPLC); optical purity 99.9 %(HPLC); specific rotation at ambient temperature in water solution -3.5° (c=20 mg/ml).

The (+)-enantiomer was resolved in the same way as the (-)-isomer using L-(+)-tartaric acid as a resolving agent to give the L-(+)-tartaric acid adduct of the (+)-enantiomer: mp 187-189 °C. The base and hydrochloride salt (mp 190 °C) were made as described above. The chromatographic purity of the hydrochloride salt was 98.7 % (HPLC); optical purity 99.6 % (HPLC); specific rotation at ambient temperature in water solution +3.2 ° (c=20 mg/ml).

CLAIMS

1. The (-)-enantiomer of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and pharmaceutically acceptable salts thereof.

2. A method for the preparation of the (-)-enantiomer of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole which comprises converting racemic 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole into a diastereoisomer salt mixture by reaction with an optically active acid, and then separating the mixture of diastereoisomeric salts by fractional crystallization and converting the separated (-)-enantiomer of the 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole salt to the free base.

3. The method according to claim 2, wherein the optically active acid is D-(-)-tartaric acid.

4. The (+)-enantiomer of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and pharmaceutically acceptable salts thereof.

5. A method for separating the (+)-enantiomer of 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole which comprises converting racemic 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole into a diastereoisomer salt mixture by reaction with an optically active acid, and then separating the mixture of diastereoisomeric salts by fractional crystallization and converting the separated (+)-enantiomer of the 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole salt to the free base.

6. The method according to claim 5, wherein the optically active acid is L-(+)-tartaric acid.

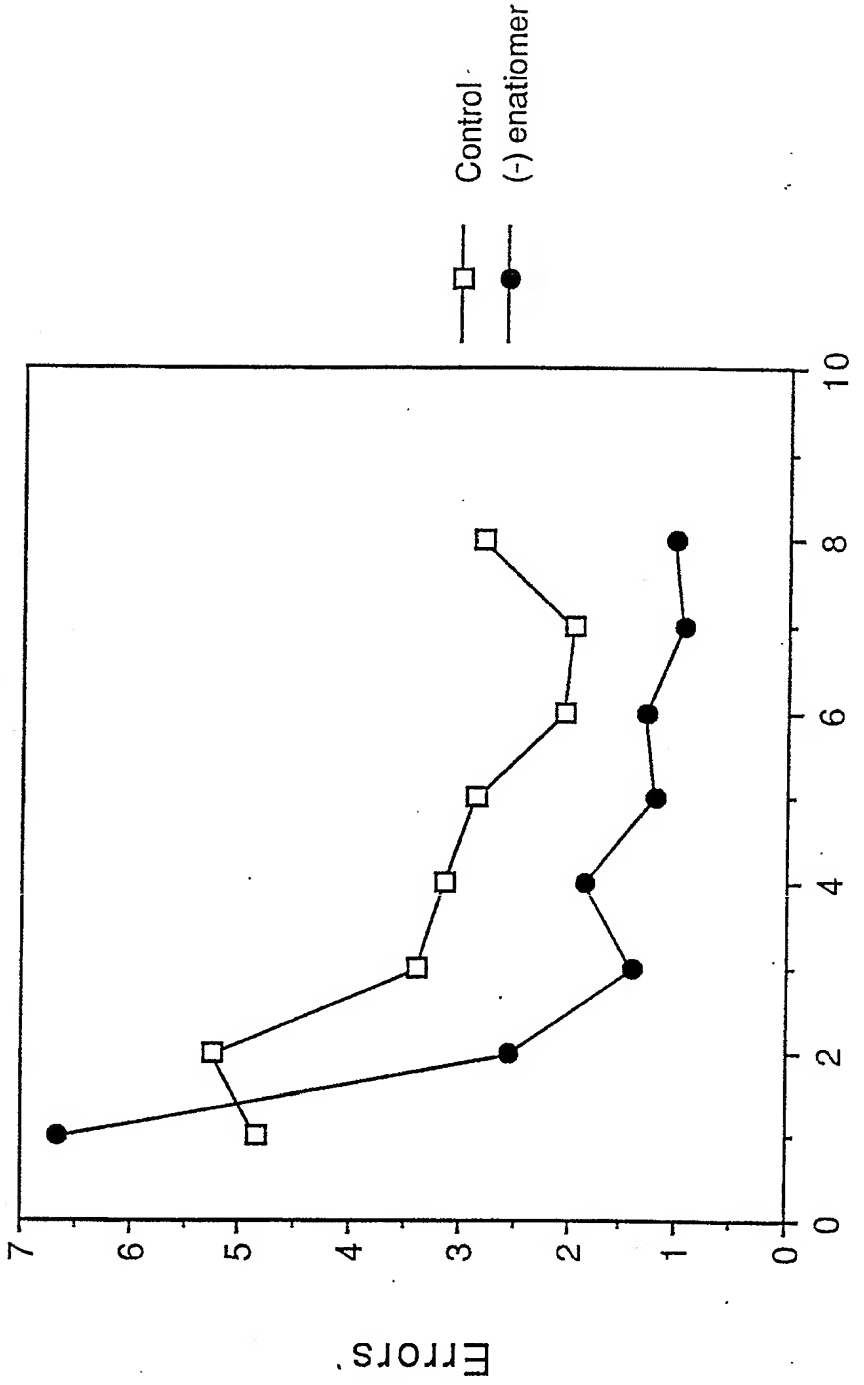

Fig 1

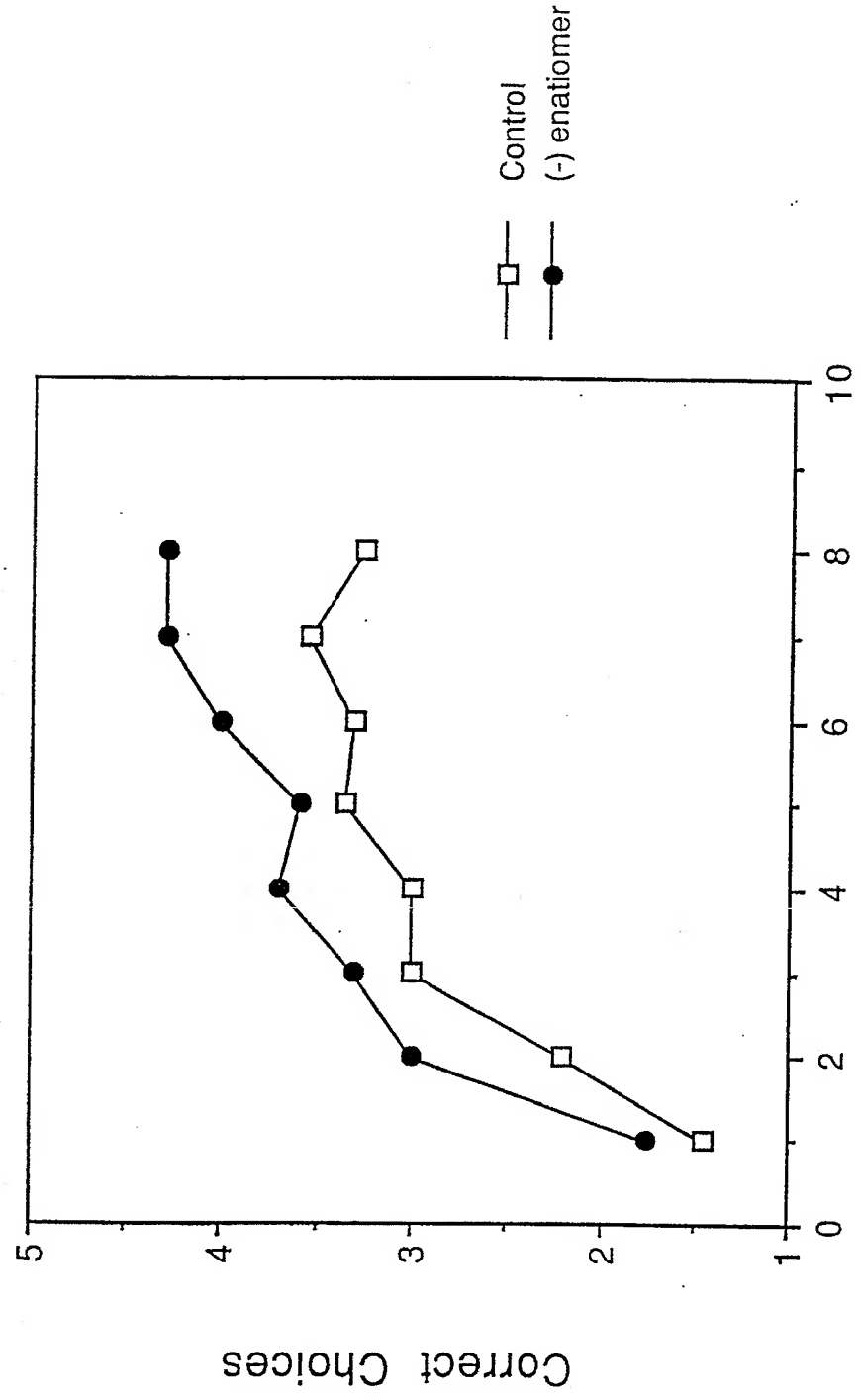

Fig 2

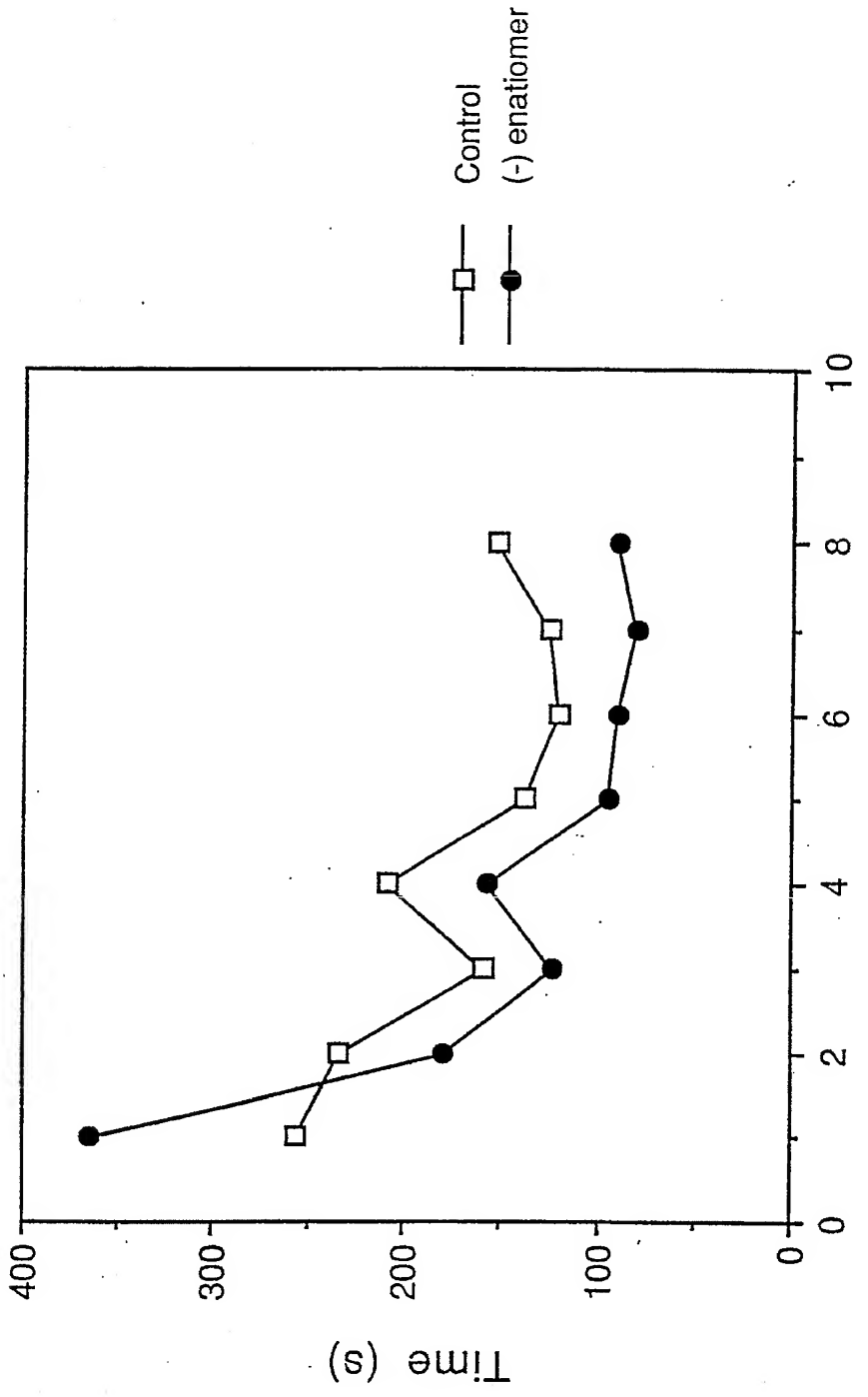

Fig 3

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D233/58 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED. CHEM. vol. 30, no. 6 , 1987 pages 1011 - 1017 J. F. DEBERNARDIS ET AL. 'Conformationally Defined Adrenergic Agents. 5. Resolution, Absolute Configuration, and Pharmacological Characterization of the Enantiomers of 2-(5,6-Dihydroxy-1,2,3,4-tetrahydro-1-naphthyl)imidazoline: A Potent Agonist at alpha-Adrenoceptors' * entire document * --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED. CHEM. vol. 29, no. 7 , 1986 pages 1183 - 1188 J. BIEDERMANN ET AL. 'Two Stereoisomeric Imidazoline Derivatives: Synthesis and Optical and alpha2-Adrenoceptor Activities' * entire document *	1-6
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A	EP,A,0 310 745 (FARMOS-YHTYMÄ OY) 12 April 1989 see claims 1-10	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

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